

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-345

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-345

Fonda BV
Attention: Richard P. Gural, Ph.D.
Vice-President, Regulatory Affairs
9 Great Valley Parkway, P.O. Box 3026
Malvern, PA 19355

Dear Dr. Gural:

Please refer to your new drug application (NDA) dated February 15, 2001, received February 15, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ARIXTRA™ (fondaparinux sodium) Injection single dose, prefilled syringe, 2.5 mg/0.5 mL.

We acknowledge receipt of your submissions dated March 15 and 21; April 5; May 1; June 15, 18, and 20; July 3, 5, 20, 25, and 31; August 1, 6, 22, and 31; September 7 and 17; October 9; November 19, 20, and 30; and December 4 and 7, 2001. Your submission of October 9, 2001 constituted a complete response to our August 15, 2001 action letter.

This new drug application provides for the use of ARIXTRA™ for the following indication: the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:

- in patients undergoing hip fracture surgery;
- in patients undergoing hip replacement surgery;
- in patients undergoing knee replacement surgery.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. The application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed package insert labeling text and the immediate container and carton labels submitted August 31, 2001. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-345." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitment in your submission dated August 31, 2001. The commitment is listed below.

- A safety evaluation of ARIXTRA™ in patients with varying degrees of impaired hemostasis secondary to hepatic insufficiency. Provide pharmacokinetic and pharmacodynamic data of ARIXTRA™ on a subset of these patients.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). As stated in our February 2, 2001 letter, we are waiving the pediatric study requirement for these indications submitted in this application.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-345

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Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Karen Oliver, Regulatory Project Manager, at (301) 827-7457.

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Package Insert Labeling Text

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-345

APPROVABLE LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-345

Fonda BV

C/O _____

Attention: Richard P. Gural, Ph.D.
Vice-President, Regulatory Affairs
9 Great Valley Parkway, P.O. Box 3026
Malvern, PA 19355

Dear Dr. Gural:

Please refer to your new drug application (NDA) dated February 15, 2001, received February 15, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ARIXTRA™ (fondaparinux sodium) single dose, prefilled syringe, 2.5 mg/0.5 mL.

We acknowledge receipt of your submissions dated March 15 and 21; April 5; May 1; June 15, 18, and 20; July 3, 5, 20, 25, and 31; and August 1 and 6, 2001.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

I. Chemistry, Manufacturing and Controls Issues:

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An acceptable response to deficiency letters issued to the holders of DMF _____ and DMF _____ on August 9 and August 13, 2001, respectively.

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II. Clinical Pharmacology Issues:

3. Provide the approximate anti-Factor Xa activity per mg of fondaparinux sodium. Include this information in the package insert to describe the pharmacodynamic properties of the drug.
4. Provide descriptive statistics (e.g., range, mean, standard deviation) of anti-Factor Xa activity achieved with fondaparinux sodium in clinical trials at the recommended fixed dose of 2.5 mg administered subcutaneously each day. Also provide these data adjusted for body weight and age.

III. Labeling Issues:

All Labeling Components

5. Provide the tradename, ARIXTRA™, with all letters of the name in the same type face and font size.
6. Provide manufacturing information (as space permits):
 - Manufactured by: Provide name and address
 - Manufactured for: Provide name and address
 - Distributed by: Provide name and address
 - Made in: Provide country

Immediate Container Label

7. Below the tradename, prominently display the following:

2.5 mg/0.5 mL

Cartons Labels and Container Tray Labels

8. Delete the following information from the upper right corner of the front and back panels:

[

]

9. Revise the phrase in the upper right corner of the front and back panels to read as follows:

10 x 0.5 mL Single Dose, Prefilled Syringes
5 x 0.5 mL Single Dose, Prefilled Syringes (professional sample)

10. After the title section, prominently display the following information:

2.5 mg/0.5 mL Single Dose, Prefilled Syringes Affixed with an Automatic Needle
Protection System
For Subcutaneous Injection

Carton Labels

11. On the front panel, delete the information in the blue box . _____

12. On the back panel, in the "Contents" section, revise the first sentence to read as follows:

Each single dose, prefilled syringe contains 2.5 mg of fondaparinux sodium in
0.5 mL of an isotonic solution of sodium chloride and water for injection.

13. On the flaps, revise the phrase _____ to
read:

10 x 0.5 mL Single Dose, Prefilled Syringes
5 x 0.5 mL Single Dose, Prefilled Syringes (professional sample)

Container Tray Labels

14. In the "Contents" section, revise the first sentence to read as follows:

Each single dose, prefilled syringe contains 2.5 mg of fondaparinux sodium in
0.5 mL of an isotonic solution of sodium chloride and water for injection.

Postmarketing (Phase IV) Commitments

We request that you commit to conduct the following postmarketing (Phase IV) studies:

[_____]

- b. A safety evaluation of ARIXTRA in patients with varying degrees of impaired hemostasis secondary to hepatic insufficiency. Provide pharmacokinetic and pharmacodynamic data of ARIXTRA on a subset of these patients.

[_____]

In addition, we request that you agree to:

[]

[]

It will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content, with additional information provided as requested in the to the enclosed labeling text, for the package insert and the submitted draft labeling (immediate container and carton labels submitted February 15, 2001) with the revisions identified above for the immediate container, container tray, and carton labels.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Karen Oliver, Regulatory Project Manager, at (301) 827-7457.

Sincerely,

(See appended electronic signature page)

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

WITHHOLD 20 PAGE (S)

Draft

Labeling

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Victor Raczkowski
8/15/01 01:39:19 PM

**APPEARS THIS WAY
ON ORIGINAL**